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## **Copy, edit, and paste: natural product approaches to biomaterials and neuroengineering**

Gademann, Karl

**Abstract:** Progress in the chemical sciences has formed the world we live in, both on a macroscopic and on a nanoscopic scale. The last century witnessed the development of high performance materials that interact with humans on many layers, from clothing to construction, from media to medical devices. On a molecular level, natural products and their derivatives influence many biological processes, and these compounds have enormously contributed to the health and quality of living of humans. Although coatings of stone materials with oils or resins (containing natural products) have led to improved tools already millennia ago, in contrast today, natural product approaches to designer materials, that is, combining the best of both worlds, remain scarce. In this Account, we will summarize our recent research efforts directed to the generation of natural product functionalized materials, exploiting the strategy of “copy, edit, and paste with natural products”. Natural products embody the wisdom of evolution, and only total synthesis is able to unlock the secrets enshrined in their molecular structure. We employ total synthesis (“copy”) as a scientific approach to address problems related to molecular structure, the biosynthesis of natural products, and their bioactivity. Additionally, the fundamental desire to investigate the mechanism of action of natural products constitutes a key driver for scientific inquiry. In an emerging area of relevance to society, we have prepared natural products such as militarinone D that can stimulate neurite outgrowth and facilitate nerve regeneration. This knowledge obtained by synthetic organic chemistry on complex natural products can then be used to design structurally simplified compounds that retain the biological power of the parent natural product (“edit”). This process, sometimes referred to as function-oriented synthesis, allows obtaining derivatives with better properties, improving their chemical tractability and reducing the step count of the synthesis. Along these lines, we have demonstrated that militarinone D can be truncated to yield structurally simplified analogs with improved activity. Finally, with the goal of designing bioactive materials, we have immobilized functionally optimized, neuritogenic natural products (“paste”). These materials could facilitate nerve regeneration, act as nerve guidance conduits, or lead to new approaches in neuroengineering. Based on the surface-adhesive properties of electron-deficient catecholates and the knowledge gathered on neuritogenic natural product derivatives, two mechanistically different design principles have been applied to generate neuritogenic materials. In conclusion, natural products, and their functionally optimized analogs, present a large, mostly untapped reservoir of powerful modulators of biological systems, and their hybridization with materials can lead to new approaches in various fields, from biofilm prevention to neuroengineering.

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# Copy, Edit, and Paste: Natural Product Approaches to Biomaterials and Neuroengineering

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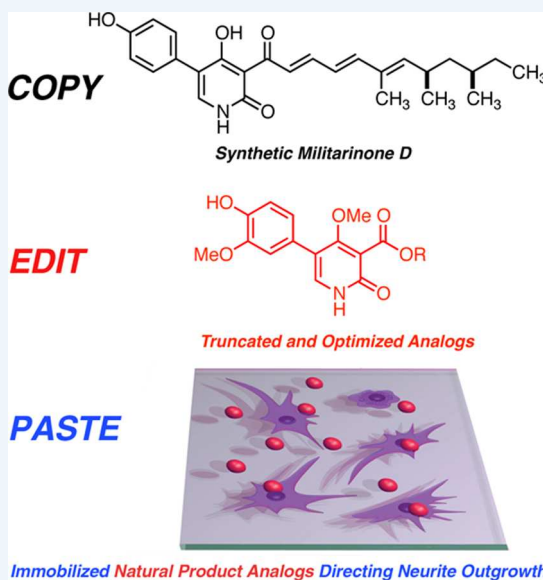
**CONSPECTUS:** Progress in the chemical sciences has formed the world we live in, both on a macroscopic and on a nanoscopic scale. The last century witnessed the development of high performance materials that interact with humans on many layers, from clothing to construction, from media to medical devices. On a molecular level, natural products and their derivatives influence many biological processes, and these compounds have enormously contributed to the health and quality of living of humans. Although coatings of stone materials with oils or resins (containing natural products) have led to improved tools already millennia ago, in contrast today, natural product approaches to designer materials, that is, combining the best of both worlds, remain scarce. In this Account, we will summarize our recent research efforts directed to the generation of natural product functionalized materials, exploiting the strategy of "copy, edit, and paste with natural products".

Natural products embody the wisdom of evolution, and only total synthesis is able to unlock the secrets enshrined in their molecular structure. We employ total synthesis ("copy") as a scientific approach to address problems related to molecular structure, the biosynthesis of natural products, and their bioactivity. Additionally, the fundamental desire to investigate the mechanism of action of natural products constitutes a key driver for scientific inquiry. In an emerging area of relevance to society, we have prepared natural products such as militarinone D that can stimulate neurite outgrowth and facilitate nerve regeneration.

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In conclusion, natural products, and their functionally optimized analogs, present a large, mostly untapped reservoir of powerful modulators of biological systems, and their hybridization with materials can lead to new approaches in various fields, from biofilm prevention to neuroengineering.



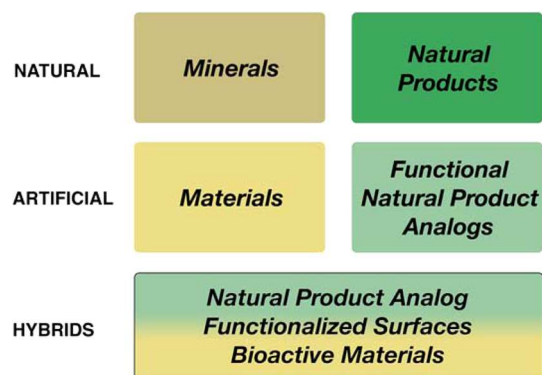
## INTRODUCTION

Materials shape the world around us. The last decades witnessed consistent development of new materials that interact with humans on many layers, from clothing to construction, from media to medical devices. On a molecular level, natural products and their derivatives influence many biological processes and interactions, between species and within them.<sup>1</sup> Humans have long utilized natural products in the form of extracts to improve the performance of their tools,<sup>2</sup> and natural product impregnated

materials had commercial success as drug eluting stents,<sup>3</sup> yet a recent perspective article raised the provocative question "Natural Product and Material Chemistries — Separated Forever?".<sup>4</sup> In this Account, we will highlight our approach to functionalized surfaces based on functionally optimized natural

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**Figure 1.** Development of hybrid materials functionalized with natural product derivatives.

products (Figure 1). These efforts draw knowledge from many fields, such as organic synthesis, chemical analysis, surface science, and cell biology, resulting in a transdisciplinary approach culminating in our recent development of neuritogenic surfaces based on natural product derivatives. The Account is structured in three main parts, each reflecting one stage of the development process along the guideline “copy, edit, and paste with natural products”.

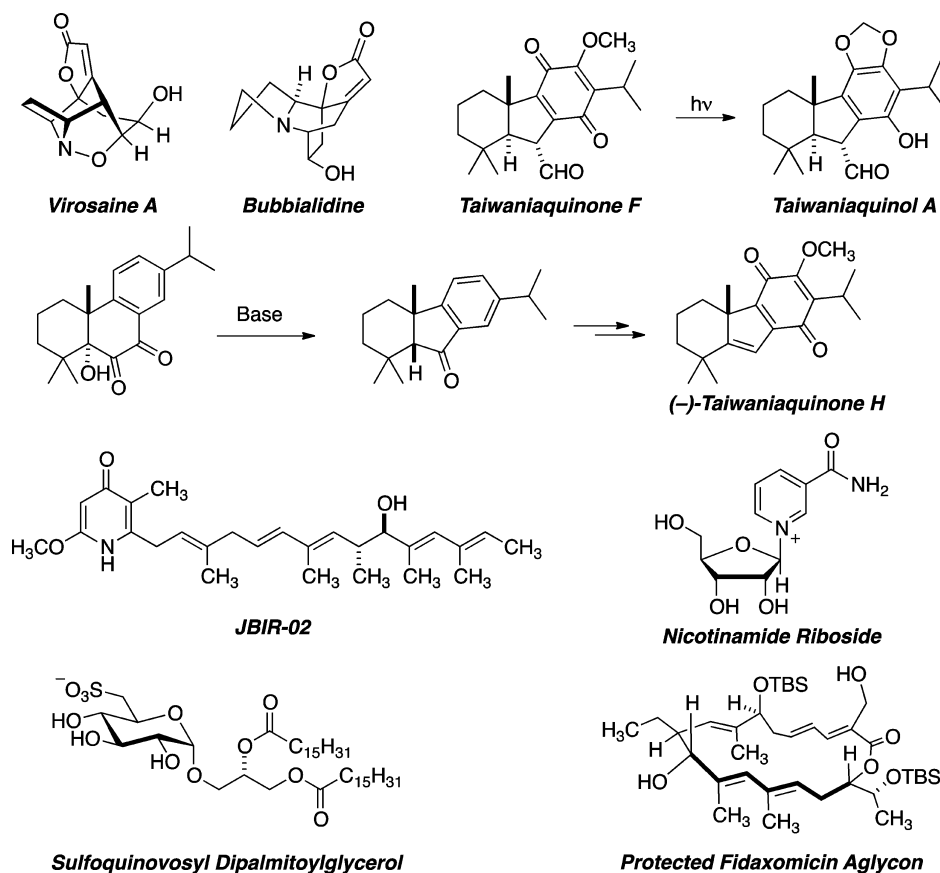
### COPY: TOTAL SYNTHESIS

According to a dictum of Nobel laureate Professor Vladimir Prelog, natural products constitute the products of billions of

years of evolution, and he called upon science to investigate their function.<sup>5</sup> The reconstitution of natural products in the chemical laboratory via total synthesis, their derivatization, and their functional optimization by synthesis<sup>6</sup> (vide infra) are excellent ways of unlocking nature’s secrets enshrined in natural products.<sup>7–9</sup> In particular, total synthesis constitutes more than a research field, as synthesis provides a scientific method to investigate problems with exceptional rigor.<sup>10</sup> For both reasons, we have established a total synthesis program to study and to understand the mechanism of action of natural products in biological systems and to evaluate unusual structures, biosyntheses, and powerful biological activities (Scheme 1).

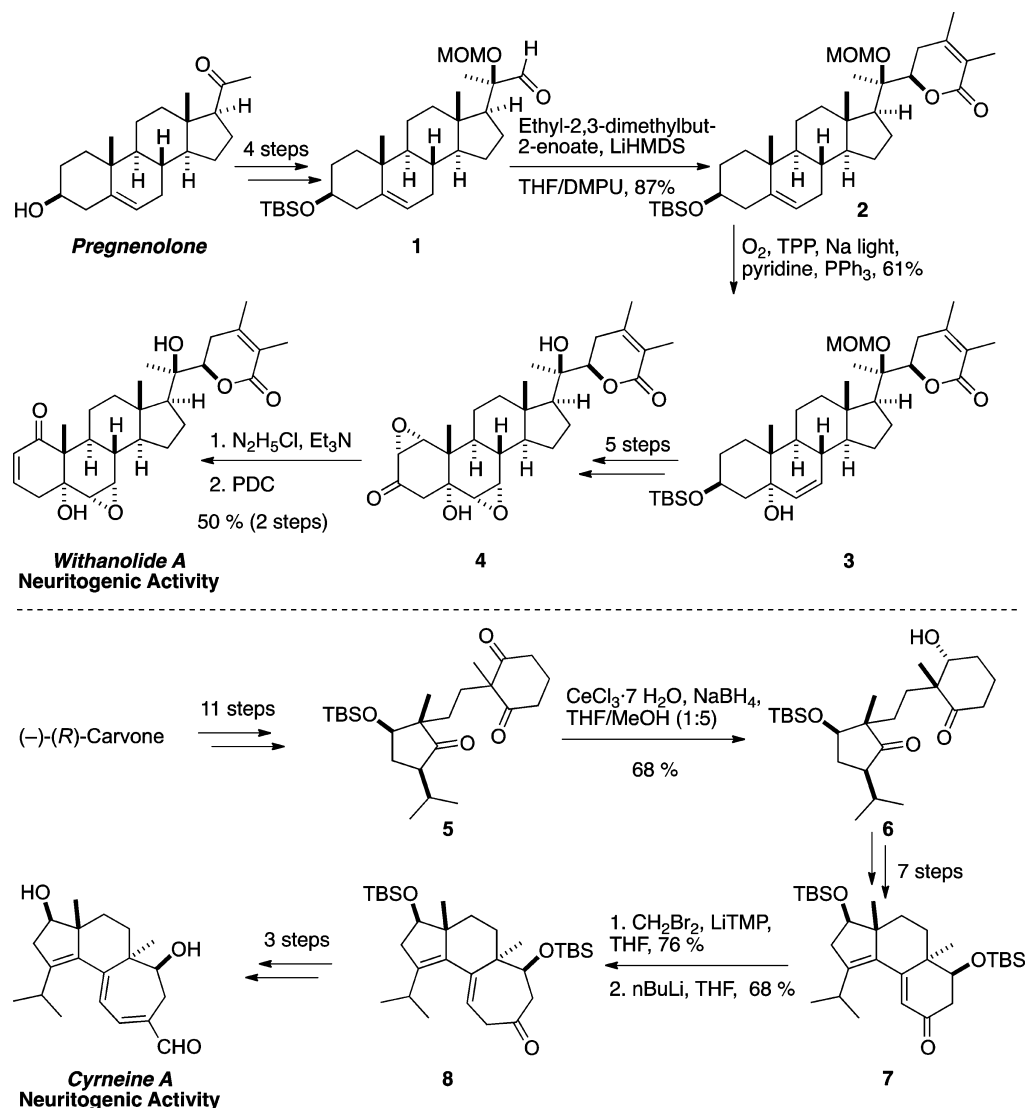
Concerning unusual structures, we were intrigued by the *Securinega* alkaloids and in particular by the birdcage-shaped virosaine. Its total synthesis and the final construction of the complex pentacyclic framework have been established via a nitron [1,3]-dipolar cycloaddition.<sup>11</sup> In the realm of unusual biosynthetic transformations, we have discovered that the diterpenoid taiwaniaquinol A can be obtained via exposure of the precursor taiwaniaquinone F to sunlight.<sup>12</sup> The mechanism of this redox-neutral process is still under investigation, but a remote C–H functionalization to furnish the 1,3-benzodioxazole ring is likely to be involved. In the taiwaniaquinoids, chemical synthesis demonstrated the feasibility of a benzylic acid rearrangement in converting C<sub>20</sub> diterpenoids to their C<sub>19</sub> congeners such as taiwaniaquinone H.<sup>13</sup> Such a process could be operative in the biogenesis of these and related compounds.<sup>14</sup> Biologically active natural products, combined with mechanism

**Scheme 1.** Total Synthesis as an Approach for Discovery<sup>a</sup>



<sup>a</sup>Natural products with unusual structures (virosaine A), provocative biogenetic hypotheses as for the taiwaniaquinones, or bioactivity have been synthesized and studied in our group.

Scheme 2. Preparation of Withanolide A and Cyrneine A



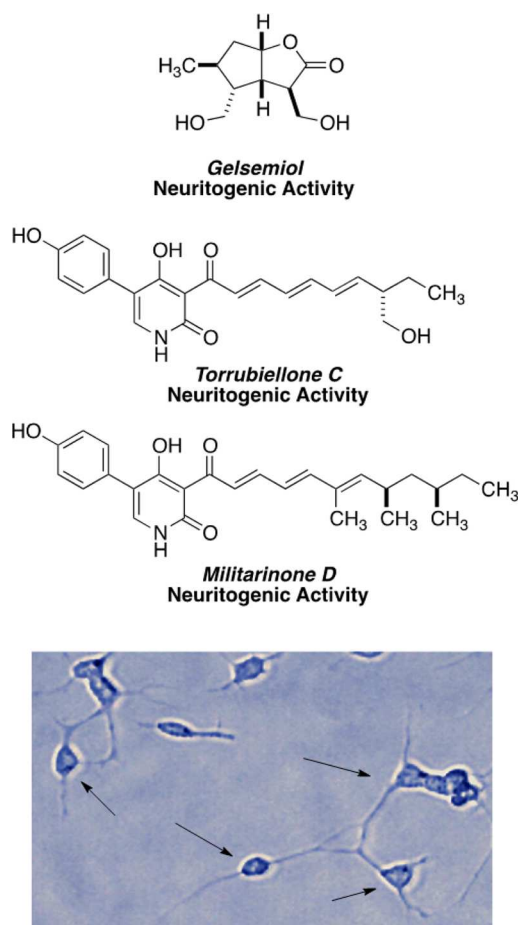
of action studies, have been a major driver for our research program. The pyridone JBIR-02, originally reported to be an inhibitor of nuclear export, has been synthesized using a stereoselective vinylogous aldol reaction, an Ir-mediated borylation/oxidation sequence for the pyridone core, and a Pd mediated coupling of an unstable 2-pyridyl Zn precursor.<sup>15</sup> Driven by biological activity, compounds such as nicotinamide riboside,<sup>16</sup> lipidated sulfoquinovose derivatives as telomerase inhibitors,<sup>17</sup> or the antibiotic fidaxomicin have prompted synthetic investigations in our group. For the last compound, we have developed a route to the aglycon en route to the natural product.<sup>18</sup>

The regeneration of neuronal networks by small molecules constitutes an active field of research, both due to the tremendous importance of this biological process for memory and learning, and also due to its relevance to neurodegenerative diseases.<sup>19</sup> Given our interest in these processes and our target of generating neuritogenic surfaces, we initiated a research program on the synthesis and biological evaluation of neuritogenic natural products (Scheme 2). Withanolide A was one of the first targets investigated, because this compound constitutes one of the active ingredients of *Ashwaganda*, a traditional Indian medicine used, among other purposes, for the improvement of cognitive

performance in the elderly. This steroid lactone has also been shown to induce neurite outgrowth in cellular models and to aid synapse reconstruction in mice.<sup>20</sup> We have prepared synthetic withanolide A starting from readily available pregnenolone (Scheme 2), using key reactions such as a diastereoselective dienophile addition to aldehyde **1** resulting in the lactone **2**, which smoothly underwent a singlet-oxygen-mediated photooxygenative olefin migration to allylic alcohol **3**. Elaboration of this intermediate to epoxyketone **4** was carried out using a protecting group-free strategy, and subsequent Wharton transposition and oxidation furnished withanolide A.<sup>21</sup> We have then carried out structure/activity relationship studies and have identified compounds with equal or higher activity by modification of the A-ring of withanolide A.<sup>22</sup> The cyathane diterpene cyrneine A has also been shown to promote neuritogenesis, which led us to embark on the total synthesis of this tricyclic trienal based on a route starting from carvone. Salient features of this synthesis include a remarkably regioselective reductive desymmetrization of trione **5** to **6**, a Heck cyclization strategy to establish the tricyclic intermediate **7**, and cycloheptenone formation to **8** via a ring expansion using a carbene rearrangement.<sup>23</sup>

The bicyclic iridoid gelsemiol displays an unusual oxidation pattern for this class of compounds, and it has been reported





**Figure 2.** Natural products promoting neurite outgrowth. Chemical total synthesis provided access to different neuritogenic natural products and biological evaluation demonstrated their potential to differentiate neuronal models, as shown in a representative image (arrows denote differentiated cells).

to potentiate the action of NGF in cellular assays (Figure 2). We have obtained synthetic gelsemiol following an approach first reported by Markó and co-workers,<sup>24</sup> which employed a Brønsted acid mediated, radical induced skeletal rearrangement to the bicycle[3.3.0] structure of the target.<sup>25</sup> Gelsemiol alone did not lead to neurite outgrowth; however, addition of gelsemiol to the neurotrophin nerve growth factor led to a significant boost in differentiation and neurite containing cells. The last compound class to be investigated for its neuritogenic properties is presented by the pyridone polyene alkaloids, such as torrubellone C or militarionone D. These red to orange colored polyenes are typically produced by entomopathogenic fungi that infect and modulate the behavior of their insect hosts.<sup>26</sup> A large number of these compounds have been isolated from insect/fungal sources from all over the world, and some structural features remain constant.<sup>26</sup> We have developed a unified synthetic access to these compounds that resulted in the total synthesis of a large number of congeners, such as torrubellone C, militarionone D, pyridovericin, and pretennelin B, as well as a number of putative natural products.<sup>27–29</sup> Interestingly, all these natural products display neuritogenic activity in the PC-12 assay. This observation prompted us to conduct a function-oriented synthesis approach for compounds with increased activity, yet reduced structural complexity, as will be discussed in the next section.

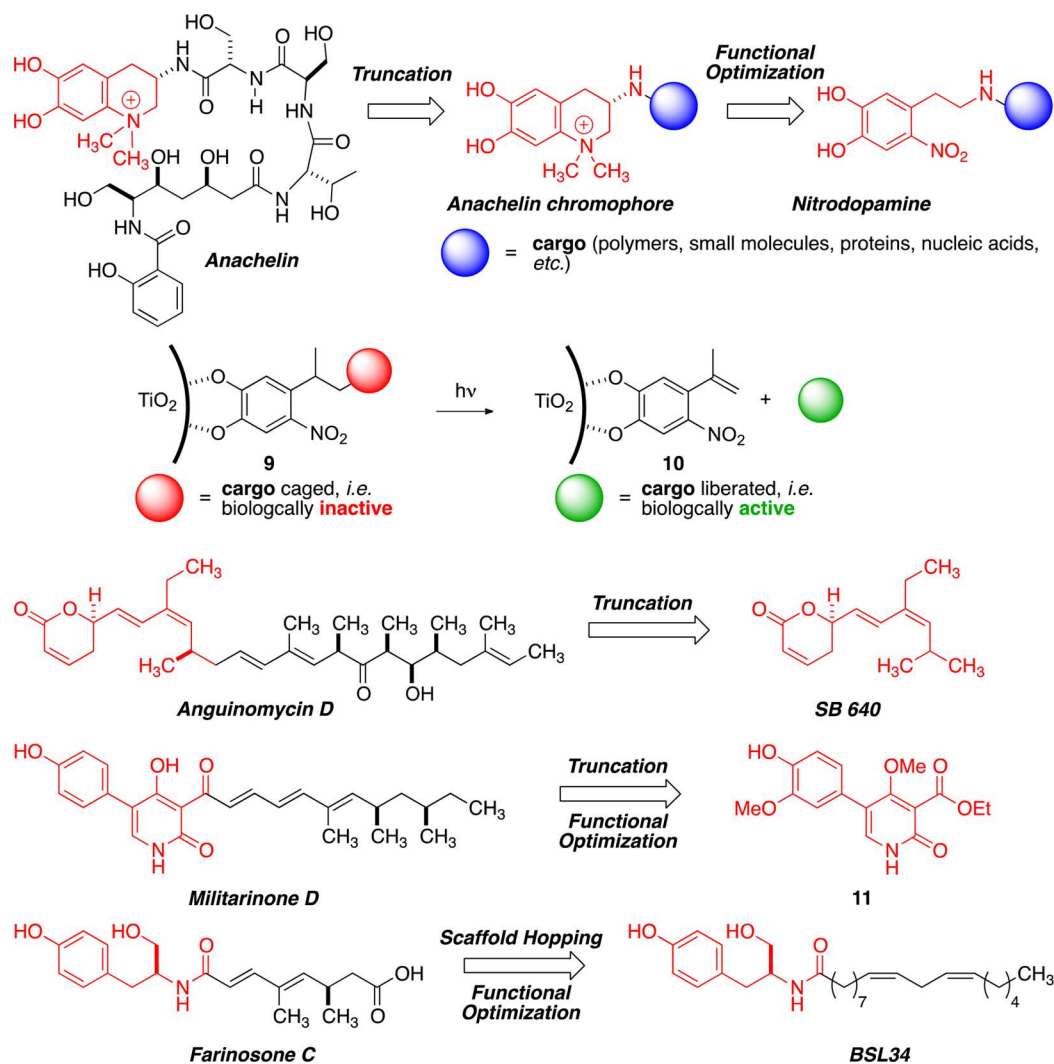
## ■ EDIT: FUNCTIONALLY OPTIMIZED NATURAL PRODUCT DERIVATIVES

In the last section, we have demonstrated that total synthesis constitutes a very powerful approach, as the power of modern methods combined with the well-established body of knowledge in the field paves the way for discovery, and, as a result, many of the target compounds have been prepared in relatively short time. The knowledge gained in these investigations can be used to characterize the most important structural features required for biological activity, which in turn can lead to structurally simplified analogs retaining their function (function-oriented synthesis).<sup>7</sup> In this section, we will discuss how we have used this approach (“reduce to the maximum”<sup>30</sup>) to obtain structurally simplified compounds with improved properties (Scheme 3).

Aquatic biofilms constitute very interesting “living materials”, because they display a multitude of interesting properties. In particular, although the robustness of surface adhesion of algae has been recognized for decades, the molecular interactions responsible for surface attachment remain mostly enigmatic. In addition, the challenge of iron acquisition of organisms in biofilms led to the hypothesis that small molecule iron chelators, so-called siderophores, bind to the mineral oxide surfaces for iron sequestration.<sup>31</sup> Because there are few complex siderophores from algae studied, we began to investigate anachelin, the complex siderophore of the cyanobacterium *Anabaena cylindrica*, and in particular, we were interested to understand whether the catecholate unit of anachelin could bind to mineral oxides, as has been hypothesized for other siderophores.<sup>32</sup> Therefore, we truncated the natural product by chemical synthesis, and coupled the anachelin chromophore (which displays a red to burgundy color) to poly(ethylene glycol) (PEG), which has been shown to generate protein resistant surfaces if densely packed. The resulting hybrid was immobilized on TiO<sub>2</sub> and a series of measurements demonstrated that the function of the parent natural product was retained in the catecholate fragment.<sup>33</sup>

After this bioinspired discovery of turning a natural product siderophore into a surface anchor, we investigated the structure–property relationship with the goal of simplifying the chemical structure while retaining its activity. Early on, and in particular when comparing it to other catecholate based systems,<sup>34–36</sup> we realized that the electron-withdrawing substituents on the aromatic system increase the stability of the catechols toward oxidation and lead to a lower pK<sub>a</sub> value, which could be of importance in surface binding. Therefore, although dopamine was prepared and utilized as a surface anchor by us,<sup>37</sup> the most promising catecholate identified along these lines was nitrodopamine.<sup>38</sup> This compound retains the electron withdrawing groups on the aromatic system with the inherent stability against oxidation and at the same time is available in only one synthetic operation from commercial dopamine.

A last useful modification consisted in the introduction of programmable release mechanisms into the catecholate systems. In this respect, “caged compounds” can be defined as molecules in which a desired property such as biological activity has been blocked by a group. On demand by the experimentalist, the caging group can then be removed by an external stimulus such as light. Such caged compounds have had a massive influence as tool compounds in biology, and we wanted to combine efficient blocking mechanisms with surface binding and release (“binding and release on demand”). The nitrobenzyl group has been identified as one of the most useful groups for caging compounds, and therefore, we set out to merge both aspects,

Scheme 3. Functionally Optimized Natural Products via Chemical Editing<sup>a</sup>

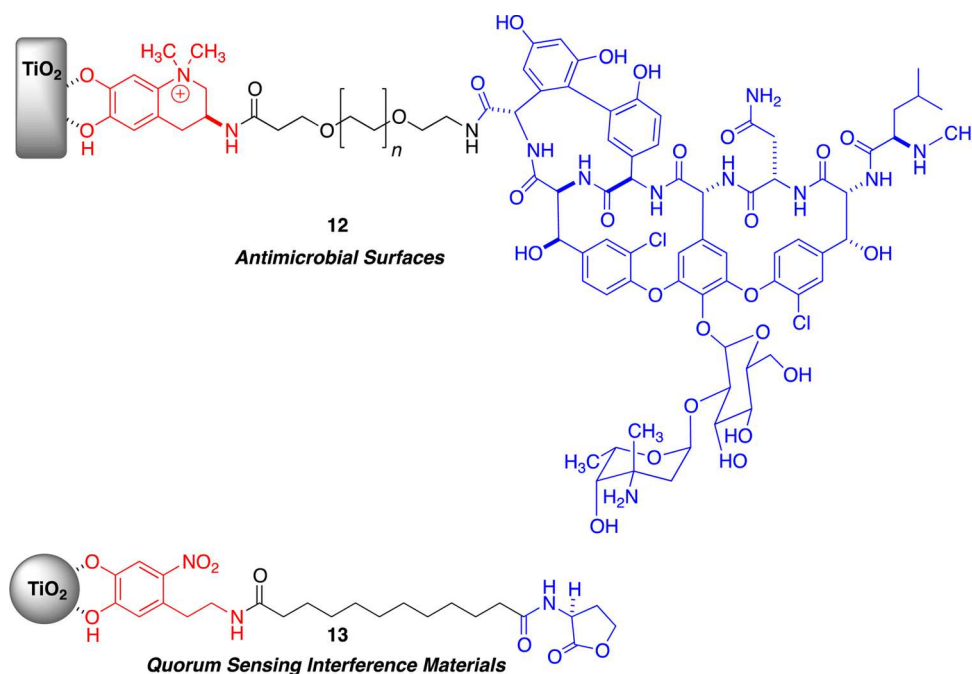
<sup>a</sup>Complex natural products with limited chemical tractability were truncated and functionally optimized by chemical synthesis to obtain structurally simplified analogs that retain their function or activity.

that is, nitrocatecholate surface modification with nitrobenzyl caging groups. The resulting precursor can be prepared in high yield in four steps, and its loading with cargo and immobilization on  $\text{TiO}_2$  particles to **9** went smoothly (Scheme 3). In this example, the red sphere represents, for example, a biologically active small molecule, a protein, etc., which is however caged due to the covalent binding to the nitrobenzyl anchor and to the surface. After adsorption, cleavage of **10** and release of the cargo within minutes from the surface was made possible via an external stimulus such as UV light ("programmable underwater bonding and release"). By this process, the green sphere is liberated and can therefore unfold its desired property.<sup>39</sup>

On a different molecular system, the polyketide anguinomycin has been shown to be a very potent antitumor agent, with a remarkable reported selectivity for transformed over normal cells.<sup>40</sup> This lactone belongs to the class of leptomycins, of which a member, callystatin, advanced to clinical trials. Because the stereogenic centers were not assigned during isolation and tempted by its powerful and selective biological activity, we began a total synthesis program that culminated in the preparation of synthetic anguinomycins C and D.<sup>41</sup> In collaboration with cell biologists, we established that these compounds shut

down nuclear export of proteins, leading to their accumulation in the nucleus. The mechanism of action has been investigated, and we proposed an atomistic model for the binding of anguinomycin to the target transporter via covalent inhibition of a key cysteine residue.<sup>41</sup> This hypothesis led to the prediction that smaller truncated analogs might retain activity, as long as some of the key features were included in the scaffold. Branching off the synthetic route, we obtained a much smaller analog, SB 640, which has been shown by biological assays to retain most of the activity of the parent compound, while being much reduced in complexity (less than half the molecular weight, only one stereocenter, less unsaturation).<sup>41</sup> This fascinating example demonstrates the power of synthetic chemistry in delivering smaller, functionally optimized compounds that retain their biological activity.

The third and most striking example is presented by the class of pyridone polyenes for which we have developed a unified synthetic route leading to many congeners of this family discussed before.<sup>27</sup> Based on the observation that the lipophilic chain length, the amount of unsaturation, and the stereogenic centers do not significantly influence the biological activity,<sup>27</sup> we opted for an unusual approach, that is complete truncation of the lipophilic side chain. The resulting phenyl pyridone core retained



**Figure 3.** Surfaces addressing microbial biofilm formation can be generated by immobilizing vancomycin or AHL derivatives.

activity, and a classical medicinal chemistry approach of evaluating the structure–activity relationship of this scaffold led to the identification of compound **11** as the most active member in this series.<sup>42</sup> Compared with the parent natural product such as militarinone, the activity was even increased by a factor of 20, while cutting the number of C atoms from 26 to 16 and reducing the number of synthetic transformations by 12.<sup>42</sup> In addition, as the polyene side chains are prone to isomerization under light and present a metabolic liability; the functionally optimized compound is devoid of these shortcomings. The often mentioned limited chemical tractability of natural products is also overcome, since the compound **11** shares many of the drug-like features and can be quickly accessed by organic synthesis. Concerning the mechanism of action of the optimized analog **11**, we could demonstrate that the MAP kinase pathway is involved, because the ERK inhibitor PD98059 leads to complete suppression of the phenotype, which is in line with the properties of the parent natural product.<sup>42</sup>

In a second, conceptually different approach, functional optimization of the inherent structural complexity of the pyridone polyenes was addressed by “scaffold hopping”, that is, replacing the pyridone scaffold with a structurally simpler, readily available unit. Again, we were inspired by the observed diversity of the natural product family, as one member, farinosone C has been isolated as a congener. Farinosone C can be considered either a shunt metabolite or of relevance to the biosynthesis of the other congeners and is structurally appealing because the pyridone core is replaced by a tyrosinol amide fused to a lipophilic chain. We have prepared and biologically evaluated farinosone C and have determined the absolute and relative configuration of the stereogenic centers.<sup>43</sup> Biological evaluation of farinosone C also established that this compound is able to induce neurite outgrowth, albeit at higher concentration compared with the pyridone congeners. The presence of this tyrosinol amide in the natural chemodiversity combined with the retained biological activity led us to postulate the hypothesis that the tyrosinol amide scaffold is functionally identical to the pyridone scaffold. In order

to evaluate this hypothesis, we prepared a series of tyrosinol amides featuring long fatty acid derived carbon chains with varying degrees of unsaturation.<sup>44</sup> Biological evaluation of these compounds revealed that some compounds retained biological activity, with the compound BSL34 being the most potent in stimulating neurite outgrowth. We have then developed a hypothesis for the mechanism of action of BSL34 based on chemical, structural, and biological reasoning. The resemblance of the chemical structure of BSL34 to endocannabinoids such as ananamide is striking, in that both compounds feature amino-ethanol moieties acylated with unsaturated fatty acids. This similarity led to the postulate that the biological activity of our compounds would be similar to naturally occurring endocannabinoids such as anandamide. Therefore, we have tested BSL34 for the inhibition of anandamide transport. Interestingly, BSL34 inhibited the putative endocannabinoid membrane transporter (EMT) with an  $EC_{50}$  value of 228 nM, which is significantly better than the current gold standard, UCM707 (1800 nM in this assay).<sup>44</sup>

In conclusion, this section demonstrated how the chemical knowledge gained in the context of a total synthesis is used to generate functionally optimized compounds that retain the biological activity of the parent natural product while being structurally simplified. In the next section, we will discuss how surfaces can be tailored and functionalized to elicit a specific biological response mediated by a functionally optimized natural product (“paste”).

## ■ PASTE: NATURAL PRODUCT FUNCTIONALIZED SURFACES DIRECTING BIOLOGICAL RESPONSE

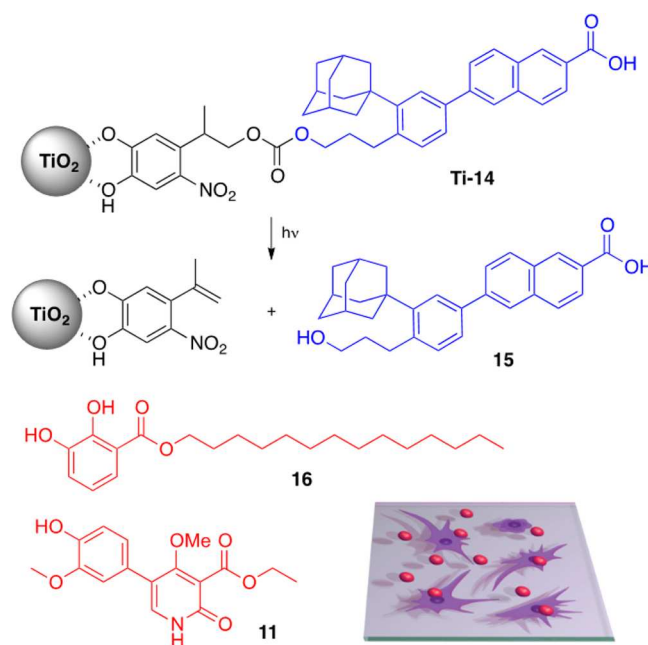
As a first application, we chose to investigate antimicrobial surfaces by immobilizing the antibiotic vancomycin on biomaterials. Infection rates related to implants, stents, and catheters in hospital settings are increasing, and the treatment of such nosocomial infections is complicated by multidrug resistant strains and encapsulation by tissue. One way of potentially addressing these issues would be the attachment of the antibiotic directly on



the medical device, and therefore rendering implants, stents, catheters or other medical instruments antimicrobial. Given the excellent adhesion properties of the anachelin chromophore as discussed above, we designed a molecular hybrid, in which the surface anchor is merged via a PEG spacer to the clinically used antibiotic vancomycin.<sup>45</sup> The resulting compound **12** was immobilized on TiO<sub>2</sub> surfaces by an operationally simple dip and rinse procedure (Figure 3). Biological assays using bacteria and live/dead staining revealed that the resulting bioactive surfaces do display antimicrobial properties, and have been shown to effectively kill bacterial cells. In addition, upon repeated exposure and rinsing, the surfaces remained bioactive, which led further experimental support to the effectiveness of the immobilized antibiotic.

As a next designer material, we wanted to target surfaces that are able to interfere with quorum sensing (QS).<sup>46</sup> This process is central in the lifestyle of many bacteria, because these organisms regulate many cellular functions based on the cellular density. This process operates on a molecular level by so-called quorum sensing modulators, of which *N*-acyl homoserine lactones (AHL) constitute one prominent class. These AHLs and derivatives have been shown to regulate QS, from induction of QS via agonistic pathways to QS blocking by synthetic agonists. Given the powerful surface modification platform developed in our group and our interest in surfaces that can prevent or address microbial infections, we wanted to immobilize AHLs with the goal of interfering with QS. As a potential application, these surfaces could interfere with bacterial biofilm formation, as the lifestyle change of some bacteria from a planktonic to biofilm forming phenotype is QS regulated. For this application, we chose the nitrodopamine surface anchor, and chemically coupled a modified AHL derivative to obtain the hybrid **13**.<sup>46</sup> These compounds could be absorbed to surfaces based on an operationally simple dip-and-rinse procedure. We then used titania microbeads for the biological assays, and, as could be determined, the resulting functionalized particles were able to interfere with QS. One advantage of the surface modification technology based on natural products is their ability to combine different bioactive natural products. For example, immobilization of both vancomycin and AHL derived hybrids on the same surface could lead to synergistic effects. This modular approach could ultimately lead to redesign the complex composition of many natural interfaces.

The regeneration of neuronal networks has been an active area of research, and in particular the regrowth of nerves along a solid support (nerve guiding, nerve conduits) has been pursued by many groups with the goal of restoring (peripheral) nerve function. In addition, because neurons are extremely efficient in the transmission and processing of information, scientists have long sought to establish a neuron/computer interface with the goal of hybridizing men and the machine. In all these investigations, scientists have relied on protein-based approaches to trigger neuronal regeneration. Given our successful research program on the synthesis and biological evaluation of small molecule, natural product-derived, and functionally optimized neuritogenic compounds, we have aimed at leveraging this knowledge by contributing and developing a small-molecule approach to nerve regenerative materials via the immobilization of neuritogenic natural product derivatives. In the following sections, we will present two approaches (1) a caged and immobilized compound that can be released to trigger neurite outgrowth with high temporal and spatial resolution and (2) a directly functionalized surface that is able to act as matrix for neuronal differentiation and regrowth (Figure 4).



**Figure 4.** Natural product approaches to biomaterials directing nerve regeneration. Compounds **16** or **11** could be directly used to coat surfaces, thus leading to neuritogenic materials inducing nerve regeneration, as shown in the schematic presentation.

The first approach combined the photocleavable surface anchor **9** that can release its cargo upon triggering by an external stimulus (see also Scheme 2). As a cargo compound, we have chosen to immobilize a synthetic retinoid, which is an analog of the vitamin A metabolite *all-trans* retinoic acid, featuring improved chemical and photophysical stability. Such retinoid derivatives are used in the clinic for a variety of skin related disorders and have been known for their powerful biological action inducing cellular differentiation. We developed the hybrid **14** featuring the photocleavable surface anchor merged to the retinoid derivative **15** via a carbonate linker.<sup>47</sup> Immobilization on titania beads was carried out using an operationally simple dip-and-rinse procedure. The resulting functionalized beads **Ti-14** have then been subjected to an external stimulus, which caused release of the agonist within minutes. Biological evaluation demonstrated the activity of the agonist **15** in triggering neurite outgrowth.<sup>47</sup> Taken together, this approach demonstrated that a neuritogenic compound can be immobilized and its activity caged. The resulting material can then be triggered by light to release the uncaged agonist, which induces neurite outgrowth.

The second design of neuritogenic materials consisted of a direct functionalization with an active compound, which would allow generating surfaces that retain activity without an external stimulus. We have screened a large variety of natural products and derivatives for these properties, and different compounds such as **16** and **11** were found to be suitable for surface modification.<sup>48</sup> While catechol **16** is a derivative of the natural product gentiside,<sup>49,50</sup> compound **11** is the functionally optimized pyridone developed earlier in our group. As optimal conditions for cellular attachment and neuronal differentiation, we identified a collagen matrix with the active compound, and surface immobilization was carried out in a DMSO/H<sub>2</sub>O mixture. After the application of this operationally simple dip-and-rinse procedure, the materials were washed and sterilized. In a series of experiments, the surfaces were incubated with neurons, and significant neuronal differentiation could be detected in the coated materials

versus the control.<sup>48</sup> This molecular approach to surface modification led to the first neuritogenic materials mediated by natural product derivatives. Potential applications of this approach could include new culture wells for neurons, peripheral nerve regeneration after injury, or the regrowth of neuronal networks on computer chips.

## CONCLUSION

We have demonstrated that total synthesis can be a powerful scientific approach for obtaining compounds of interest and to understand structural requirements for bioactivity. In particular, we have been interested in natural products that can stimulate neurite outgrowth and nerve regeneration. Exploiting this knowledge led to the design and synthesis of smaller compounds with reduced structural complexity that retain or even feature improved activity. Examples of this approach discussed include (1) optimization of an iron chelator to arrive at nitrodopamine, which has been shown to be a powerful anchor group for metal oxides, and (2) truncation of polyene pyridones to yield structurally simplified analogs with improved neuritogenic activity. In the last section, we have demonstrated how a surface can be functionalized with natural products resulting in bioactive materials. In particular, we have developed (1) surface modification protocols that led to antimicrobial and quorum sensing interference surfaces and (2) neuritogenic materials that can stimulate nerve regeneration. Potential applications of these approaches could be related to medical devices, the man/machine interface, or neuroengineering.

## AUTHOR INFORMATION

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### Notes

The authors declare no competing financial interest.

### Biography

**Karl Gademann** (1972) was educated at ETH Zürich and Harvard University and worked with Prof. Dieter Seebach, Prof. Eric N. Jacobsen, and Prof. Erick M. Carreira. His first professorial appointment was at the EPFL Lausanne, and Karl Gademann currently holds a chair at the University of Basel as a full professor. He has been elected to the board of the Swiss Academy of Sciences and is affiliated with the National Centres of Competence in Research “Chemical Biology” and “Molecular Systems Engineering”. Karl Gademann will move in the summer of 2015 to the University of Zürich. His work has been recognized by a number of international awards, including the Latsis prize, the Novartis Early Career Award, the Ruzicka Medal, and the European Young Investigator Award.

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